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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Gary P Oakeson
Thorpe North & Western
PO Box 1219
Sandy, UT 84091

EXAMINER	
STONE, CHRISTOPHER R	
ART UNIT	PAPER NUMBER
1609	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,273	DAFTARY ET AL.	
	Examiner	Art Unit	
	Christopher R. Stone	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 27-52 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 27-52 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 51 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27,31-52 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses chemicals, such as the compounds of claim 2, which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claim(s) 27,31-52 are directed to encompass all oxazaphosphorine

compounds, which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these compounds (other than the compounds of claim 2) meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed derivatives, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Finally, University of California v. Eli Lilly and Co.,

43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 4 1 USPQ2d at 1966.

Therefore, only the above chemically structurally defined chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115.)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 51 provides for the use of a stable oxazaphosphorine-containing composition as defined in claim 50 in the manufacture of a medicament for the treatment of a malignant disease, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-29, 31-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Cserati and Hollo) in view of (Links and Lewis).

Cserati and Hollo discloses a composition comprising cyclophosphamide (cytoxan), hydroxypropyl-β-cyclodextrin, and water (p.70, 1st column, lines 28-34, 2nd column, lines 3-6.) Cserati and Hollo further discloses that cyclodextrins increases the stability of guest molecules (p. 70, 1st column, line 4 and 5 and p.71, Table 1, Number 16.) Cserati and Hollo does not disclose the aforementioned composition further comprising mesna. Links and Lewis discloses that mesna is a commonly used chemoprotective agent in patients receiving ifosfamide and cyclophosphamide (p.305, 2nd column, lines 1-3.) Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention, motivated by the desire to treat oxazaphosphorine-induced toxicity, to add mesna to the composition of cyclophosphamide, hydroxypropyl-β-cyclodextrin, and water thus resulting in the practice of the instantly claimed invention with a reasonable expectation of success. It also would have been obvious to a person of ordinary skill in the art at the time of the invention to prepare the composition by adding cyclophosphamide and mesna (as such or as an aqueous solution optionally containing a etherified β-cyclodextrin) to an aqueous solution of hydroxypropyl-β-cyclodextrin to maintain the stability of the compounds. Mixing and making up the volume with water would have been obvious to a person of ordinary skill in the art at the time of the invention as well.

The optimization of composition components would have been obvious to one of ordinary skill in the art at the time of the invention. Optimization of the molar substitution of Hydroxypropyl-β-cyclodextrin would have been desired to acquire favorable solubility and complex formation. Optimization of Hydroxypropyl-β-cyclodextrin content would

have been desired for optimal stability of the composition. Optimization of oxazaphosphorine concentration would have been desired for optimal therapeutic effect. Optimization of the oxazaphosphorine to mesna ratio would have been desired to ensure optimal therapeutic effect with minimal urotoxicity.

The addition of parenteral additives to the composition at any step in the preparation would have been obvious to one of ordinary skill in the art at the time of the invention. The addition of additives such as buffers, diluents and chelators would have been desired to adjust the pH, to maintain the pH, to adjust the volume, to adjust the concentration, and to further increase stability.

Filter sterilizing the composition, aseptically filling it into sterile containers and sealing the containers would have been obvious to one of ordinary skill in the art at the time of the invention. Sterility would have been desired to avoid infection caused by contaminants in the composition. Using filter sterilization would have been particularly desirable since other sterilization techniques involve heating, which may deteriorate composition components.

Ifosfamide and cyclophosphamide were commonly used cancer drugs at the time of the invention. Therefore it would have been obvious to one of ordinary skill at the time of the invention to use the instantly claimed composition to treat a malignant disease because the therapeutically active oxazaphosphorine compounds were already commonly used for this purpose.

Claim 27, 28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Cserati and Hollo), in view of (Links and Lewis) and (Baumann and Preiss).

Cserati and Hollo and Links and Lewis disclose the aforementioned inventions, but they do not disclose the composition of the instantly claimed invention comprising ifosfamide. However, the composition of the instantly claimed invention comprising the oxazaphosphorine compound cyclophosphamide is disclosed. Baumann and Preiss discloses that cyclophosphamide and ifosfamide are the two most commonly used oxazaphosphorine compounds (p. 174, 1st column, lines 7-8.) The two compounds are isomers and share a very similar structure. Thus it would have been obvious to one of ordinary skill in the art at the time of the instant invention to use either oxazaphosphorine compound (cyclophosphamide or ifosfamide) in the composition of Cserati and Hollo and to add mesna, since both compounds cause bladder toxicity. Thus resulting in the practice of the claimed invention with a reasonable expectation of success.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 27-50 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-38 of U.S. Patent No. 7199111 in view of (Links and Lewis) and (Baumann and Preiss). Claims 1-38 of U.S. Patent No. 7199111 are drawn to an aqueous ifosfamide composition comprising ifosfamide and hydroxypropyl-β-cyclodextrin optionally containing parenteral additives and the process of preparing the sterile product. Claims 1-38 of U.S. Patent 7199111 do not specify the composition containing the oxazaphosphorine compound cyclophosphamide in place of ifosfamide or the composition further comprising mesna. Baumann and Preiss discloses that cyclophosphamide and ifosfamide are the two most commonly used

oxazaphosphorine compounds in chemotherapy (p. 174, 1st column, lines 7-8.) The two compounds are isomers and share a very similar structure. Thus it would have been obvious to one of ordinary skill in the art at the time of the instant invention to use either oxazaphosphorine compound (cyclophosphamide or ifosfamide) in the composition. Links and Lewis discloses that mesna is a commonly used chemoprotective agent in patients receiving ifosfamide and cyclophosphamide (p.305, 2nd column, lines 1-3.) Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention, motivated by the desire to treat oxazaphosphorine-induced toxicity, to add mesna to the composition of an oxazaphosphorine, hydroxypropyl-β-cyclodextrin, and water thus resulting in the practice of the instantly claimed invention with a reasonable expectation of success.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Bhardwaj et al 'Approaches to Reducing Toxicity of Parenteral Anticancer Drug Formulations Using Cyclodextrins' PDA Journal of Pharmaceutical Science and Technology vol. 54(3), p. 233-239, 2000.

This reference discloses the use of hydroxypropyl-β-cyclodextrin to decrease the toxicity associated with the administration of the anticancer drug Mitomycin C.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher R. Stone whose telephone number is (571)

270-3494. The examiner can normally be reached on Monday-Thursday, 7:30am-4:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

30July2007
CRS

CECILIA TSANG
SUPERVISORY PATENT EXAMINER